Request for Continued Examination

Applicants hereby request continued examination of this application. Applicants respectfully request that the current Amendment be entered and considered.

Claims 10, 19-36, 41 and 42 were previously withdrawn from consideration as being drawn to a non-elected invention and species. Claims 37, 39 and 40 were previously canceled and claims 43 - 45 were previously presented. Claims 1, 3, 4, 17 and 18 were previously amended.

35 USC 103(a) Rejections

Claims 1-9, 12-18 and 38 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US2003/0072754), Kirk et al. (US2002/0119150), Storb et al. (Blood 94: 2523-2529) and Heeman et al. (Transplant Immunology 4: 64-67, 1996). Applicants respectfully disagree.

The examples found in all of the references cited above report results of studying one agent (anti-CD154 only in Kenyon et al) or combinations utilizing CTLA4Ig and one other agent (CTLA4Ig + MR1 or cyclosporine in Larsen et al.; CTLA4Ig + 5c8 in Kirk et al.; CTLA4Ig + MMF in Storb et al.; CTLA4Ig + LFA-1 in Blazer et al.) in the treatment of transplant rejection. None of the references report data of studies utilizing more than two agents.

The Applicants and the cited art demonstrate that the inhibition of immune responses resulting from the blockade of the CD28/CTLA4/B7 and CD40/CD154, or CD28/CTLA4/B7 and blockers of adhesion molecule-mediated interaction pathway can be potent. However, applicants and newly cited art further demonstrate that the inhibition of immune responses resulting from these pathways may be incomplete in some cases. For instance, Lehnert and co-workers report that the blockade of said pathways results in the acceptance of pig and rat islet xenografts but not rat cardiac grafts in mice (Transplant Immunology 9 (2001) 51-56; copy enclosed). Also, Trambley and co-workers describe that BALB/c-, C57BL/6 murine skin transplants, another model of allogeneic transplantation, are resistant to CD28+CD154 blockage (The Journal of Clinical Investigation (1999) 1715-1722, copy enclosed; see also the present specification at page 4. lines 1 to 4). This situation is also reflected by the experimental data contained in the present specification. As shown in Example 2, the combined blockage of the CD28/CTLA4/B7 and CD40/CD154 pathways by administering soluble CTLA4Ig and anti-CD40L (MR1) leads to very long-term graft survival of murine neonatal heart to ear transplants, while the addition of a third agent does not provide an additional benefit. Based on the above references and experiments, one knowledgeable in the art would not be able to predict the results of combining a third agent to the double combination

therapy prior to performing the experiments described in Example 1. Example 1, in contrast to Example 2, shows that the same treatment does not provide long-term graft survival of murine tail skin transplants, but demonstrates that the addition of third agent, as claimed, is surprisingly more effective than the double therapy described in the cited art.

Storb et al. only reinforces the double therapy pathway described in Blazer et al., Kirk et al., Keynon et al. and Larsen et al. If Blazer is considered in view of Larsen, Kirk, Kenyon, and Storb and the basic principles set forth in Strom et al. and Heeman, the skilled person would not consider adding a third agent to a double therapy that is performing adequately and would not be able to predict the outcome of the addition of a third agent to an inadequately performing double therapy.

In view of the lack of evidence showing the claimed invention is obvious in view of the cited references, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-9, 12-18 and 38, under 35 USC 103(a).

Claims 6, 8 and 11 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754), Kirk et al. (US 2002/0119150) Storb et al. (Blood 94: 2523-2529) and Heeman et al. (Transplant Immunology 4: 64-67, 1996) as applied to claims 1-9, 12-18 and 38 above and further in view of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40 antibiotics and anti-LFA-1 antibodies as acknowledged on pages 15-16 of the instant specification and cited in published references. Applicants respectfully disagree.

Since Blazer et al., in view of Larsen et al., Strom et al., Kenyon et al., Kirk et al., Storb et al. and Heeman et al. do not render obvious the claimed methods for the reasons discussed above, the fact that reagents of the claimed methods were publicly available does not provide the motivation to one skilled in the art to combine the three claimed agents with or without the standard of practice immunosuppression agents described by Strom.

Accordingly, the Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 6, 8 and 11, under 35 USC 103(a).

Claims 6 and 43-45 are rejected under 35 USC 103(a) as being unpatentable over Blazer et al. (WO95/34320) in view of Larsen et al. (US patent 5,916,560), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996, pages 451-456), Kenyon et al. (US 2003/0072754) and Kirk et al. (US 2002/0119150), Storb et al. (Blood 94: 2523-2529) and

Heeman et al. (Transplant Immunology 4: 64-67, 1996) as applied to claims 1-9, 12-18 and 38 above and further in view of Peach et al. (US2003/0219863).

Since Blazer et al., in view of Larsen et al., Strom et al., Kenyon et al., Kirk et al., Storb et al. and Heeman et al. do not render obvious the claimed methods for the reasons discussed above, the substitution of L104EA29YIg for CTLA4Ig in the double combination therapy taught by Blazer et al. actually teaches away from the benefit of adding a third agent to the double combination therapy. Since L104EA29YIg has higher binding avidity compared to CTLA4Ig, the L104EA29YIg double combination therapy would be expected to be more effective than the CTLA4Ig double combination therapy. Therefore one knowledgeable in the art would not be motivated to add a third agent, which would risk increasing the potential for toxicity.

Applicants respectfully request the Examiner to reconsider and withdraw the above rejections. The Commissioner is authorized to charge Deposit Account 19-3880 (Bristol-Myers Squibb Company) for any requisite fees due or to credit any overpayment. The Examiner is invited to contact the undersigned if there are any questions relating to the prosecution of this application.

Respectfully submitted,

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